Diabetes and the Brain

Edited by

Geert Jan Biessels

José A. Luchsinger

Humana Press

DIABETES AND THE BRAIN

Edited by

Geert Jan Biessels, MD, PhD
University Medical Center, Utrecht, The Netherlands

Jose A. Luchsinger, MD, MPH
Columbia University College of Physicians and Surgeons,
New York, NY, USA

Humana Press

Editors
Geert Jan Biessels
Department of Neurology
Rudolf Magnus Institute of Neuroscience
University Medical Center Utrecht
PO Box 85500
Utrecht
3508 GA Utrecht
The Netherlands
g.j.biessels@umcutrecht.nl

Jose A. Luchsinger
Columbia University
Medical Center
Presbyterian Hospital
622 West 168th St.
New York, NY 10032
USA
jal94@columbia.edu

ISBN 978-1-60327-849-2 e-ISBN 978-1-60327-850-8
DOI 10.1007/978-1-60327-850-8

Library of Congress Control Number: 2009933948

Printed on acid-free paper

springer.com

CONTEMPORARY DIABETES

ARISTIDIS VEVES, MD, DSc

SERIES EDITOR

The Diabetic Foot: *Second Edition,* edited by *Aristidis Veves, MD, John M. Giurini, DPM, and Frank W. LoGerfo, MD, 2006*

The Diabetic Kidney, edited by *Pedro Cortes, MD* and *Carl Erik Mogensen, MD, 2006*

Obesity and Diabetes, edited by *Christos S. Mantzoros, MD, 2006*

Diabetic Retinopathy, edited by *Elia J. Duh, MD, 2008*

Diabetes and Exercise: edited by *Judith G. Regensteiner, PhD, Jane E.B. Reusch, MD, Kerry J. Stewart, EDD, Aristidis Veves, MD, DSc, 2009*

Diabetes and the Brain, edited by *Geert Jan Biessels, MD, PhD, Jose A. Luchsinger, MD, MPH*

Preface

Diabetes, particularly type 2 or adult onset diabetes, is increasing in prevalence in the world. In the United States the prevalence of diabetes is over 12% in persons of age 60 years and older. The prevalence in Europe is 8–10% and catching up with the United States. The trend worldwide is for this prevalence to increase given the epidemic of overweight and obesity (2/3 of the adult United States population is overweight or obese). Thus, the fact that diabetes affects the brain is of enormous public health importance.

While acute cerebral complications of diabetes, such as hypoglycemia or stroke, are well recognized, more chronic cerebral conditions, such as cognitive and mood disorders, have failed to be recognized until recently. The last few decades have yielded new insights linking type 2 diabetes to dementia and other cognitive disorders and into the cognitive consequences of type 1 diabetes. Hence, the impact of diabetes on the brain has become a very multifaceted topic. Clinical care and research on cerebral complications of diabetes now involve internists, neurologists, psychiatrists, psychologists, and basic scientists. There has been a surge in pre-clinical and clinical research papers ranging from topics such as management of hyperglycemia in acute stroke to disturbances in insulin signaling in Alzheimer's disease. This has led to substantial progress in the field, but it also makes it more difficult for those involved to keep track of all relevant developments.

This book provides an update on the acute and chronic consequences of diabetes in the brain. We brought together experts from around the world in order to provide a helicopter view of this intriguing topic. The book offers not only in-depth reviews on cerebral complications of diabetes, but also introductory chapters on current insights into the pathophysiology and clinical management of diabetes and its complications and on stroke, neuropsychological assessment and dementia. With these "update on diabetes for neurologists" and "update on stroke and dementia for diabetologists" we hope to offer relevant and easily accessible background information that puts the cerebral complications of diabetes into context.

The target audience of this book is broad and includes medical specialists taking care of persons with diabetes and researchers in the diabetes field. It is important to point out that most clinicians and researchers think that the only complications of diabetes are microvascular (retinopathy, renal, neuropathy) and macrovascular (heart disease and stroke). Given increased longevity, the

aging of our societies, and the increasing prevalence of diabetes, the chronic consequences of diabetes in the brain are at least as important but have failed to acquire the recognition that more traditional complications have. We believe that this book will bring the consequence of diabetes in the brain to the mainstream and thus has the potential to change the field.

We thank Aristidis Veves, from Harvard Medical School, Boston, for inviting us to put together this book for the Humana Press "Contemporary Diabetes" series, for which he is the series editor. We would also like to thank Paul Dolgert and Connie Walsh from Springer Science and Business Media for their help and support. Finally, we thank the authors, all internationally distinguished in their fields, for their invaluable contributions to this book.

Geert Jan Biessels
José A. Luchsinger

Contributors

GEERT JAN BIESSELS • *Department of Neurology, G03.228, Rudolf Magnus Institute of Neuroscience, University Medical Center, 3508 GA Utrecht, The Netherlands,* g.j.biessels@umcutrecht.nl

AUGUSTINA M.A. BRANDS, *PhD • Regional Psychiatric Centre/Zuwe Hofpoort Hospital, Woerden, The Netherlands; Helmholtz Institute, Utrecht University, Utrecht, The Netherlands,* i.brands@altrecht.nl

SUZANNE CRAFT, *PhD • Veterans Affairs Puget Sound, University of Washington, Geriatric Research, Education, and Clinical Center, Seattle, WA 98108, USA,* scraft@u.washington.edu

SUSANA EBNER, *MD • Medicine Department, Columbia University, New York, NY, USA,* sae2103@columbia.edu

HERMES JOSE FLOREZ, *MD, MPH, PhD • Associate Professor of Clinical Medicine and Epidemiology, Clinical Director Geriatric Research, Education and Clinical Center (GRECC), University of Miami Miller School of Medicine, Miami Veterans Affairs Healthcare System, Medicine Department, Divisions of Endocrinology and Geriatric Medicine, Miami, FL, USA,* hflorez@med.miami.edu

MATTHEW FREEBY, *MD • Department of Medicine, Columbia University, New York, NY, USA,* mf2314@columbia.edu

BRIAN M. FRIER, *BSc (Hons), MD, FRCP (Edin), FRCP (Glas) • Diabetes Department, Edinburgh, Scotland EH16 4SA, UK,* brian.frier@luht.scot.nhs.uk

RAJIV A. GANDHI, *MBChB, MRCP • Sheffield Teaching Hospitals, NHS Trust, Diabetes, Sheffield S10 2JF, UK,* rajiv.gandhi@sth.nhs.uk

L. JAAP KAPPELLE • *Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, 3584 CX Utrecht, The Netherlands,* l.kappelle@umcutrecht.nl

ROY P.C. KESSELS • *Radboud University Nijmegen, Donders Centre for Cognition, 6500 HE Nijmegen, The Netherlands; Helmholtz Institute, Utrecht University, The Netherlands; Donders Institute for Brain,*

Cognition and Behaviour, Radboud University Nijmegen and Radboud University Nijmegen Medical Centre, Nijmesen, The Netherlands, r.kessels@ger.umcn.nl, r.kessels@donders.ru.nl

NYIKA D. KRUYT, *MD • Department of Neurology, University of Amsterdam, 1100 DE Amsterdam, The Netherlands,* n.d.kruijt@amc.uva.nl

MARIA D. LLORENTE, *MD • Chief, Psychiatry Service, Miami VA Healthcare System, Miller School of Medicine, University of Miami, Miami, FL, USA,* maria.llorente@med.va.gov

JOSÉ ALEJANDRO LUCHSINGER, *MD, MPH • Florence Irving Associate Professor of Medicine and Epidemiology, Gertrude H. Sergievsky Center, Columbia Univeristy Medical Center, New York, NY, USA,* jal94@columbia.edu

JULIE E. MALPHURS, *PhD • Health Science Specialist, Miami VA Healthcare System, Assistant Professor of Psychiatry, Miller School of Medicine, University of Miami, Miami, FL, USA, julie.malphurs@va.gov*

BORIS N. MANKOVSKY, *MD • Institute of Endocrinology, Kiev Ukraine,* mankovsky1964@yahoo.com

JENNIFER B. MARKS, *MD • University of Miami Miller School of Medicine, Miami Veterans' Affairs Medical Center, Miami, FL, USA,* jmarks@miami.edu

YAEL D. REIJMER • *Department of Neurology, G03.228, Rudolf Magnus Institute of Neuroscience, University Medical Center, 3508 GA Utrecht, The Netherlands, y.d.reijmer@umcutrecht.nl*

YVO W.B.M. ROOS, *MD, PhD • Department of Neurology, H2-218, Academic Medical Centre, University of Amsterdam, 1100 DE Amsterdam, The Netherlands,* Y.B.Roos@amc.uva.nl

CHRISTOPHER M. RYAN, *PhD • Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA,* ryancm@upmc.edu

ALEX AURELIO SANCHEZ, *MD • Advanced Geriatrics Fellow, University of Miami Miller School of Medicine, Medicine Geriatrics, Miami, FL, USA,* carot732003@yahoo.com

PHILIP SCHELTENS, *MD, PhD • VU University Medical Center, Alzheimer Center, Department of Neurology, Amsterdam 1007 MB, The Netherlands,* p.scheltens@vumc.nl

DINESH SELVARAJAH, *MBChB, MRCP* • *University of Sheffield, Diabetes Research, Royal Hallamshire Hospital, Sheffield S102JF, Yorkshire, UK,* dinesh.selvarajah@sth.nhs.uk

ANDERS A.F. SIMA • *Department of Pathology, Wayne State University School of Medicine, Detroit, MI 48201, USA,* asima@med.wayne.edu

ALINE M.E. STADES, *MD, PhD* • *Department of Internal Medicine, University Medical Center Utrecht, Utrecht, The Netherlands,* A.Stades@umcutrecht.nl

EDITH W.M.T. TER BRAAK, *MD, PhD* • *Department of Internal Medicine, University Medical Center Utrecht, Utrecht, The Netherlands,* e.terbraak@umcutrecht.nl

SOLOMON TESFAYE, *MD, FRCP* • *Diabetes Department, Sheffield Teaching Hospitals, Sheffield S10 2JF, Yorkshire, UK,* solomon.tesfaye@sth.nhs.uk

ESTHER VAN DEN BERG • *Department of Neurology, G03.228, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, 3508 GA Utrecht, The Netherlands,* e.vandenberg-6@umcutrecht.nl

WIESJE M. VAN DER FLIER, *PhD* • *VU University Medical Center, Alzheimer Center, Department of Neurology, Department of Epidemiology and Biostatistics, Amsterdam 1007 MB, The Netherlands,* wm.vdflier@vumc.nl

LAURA A. VAN DE POL, *MD* • *VU Medical Centre, Department of Neurology, 1007 MB Amsterdam, The Netherlands,* l.vandepol@vumc.nl

H. BART VAN DER WORP, *MD, PhD* • *Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, 3584 CX Utrecht, The Netherlands,* h.b.vanderworp@umcutrecht.nl

G. STENNIS WATSON, *PhD* • *University of Washington, Psychiatry and Behavioral Sciences, Seattle, WA 98108, USA,* gswatson@u.washington.edu

IAIN D. WILKINSON, *MSc, PhD, FIPEM, ARCP* • *University of Sheffield, Academic Radiology, Royal Hallamshire Hospital, Sheffield S102JF, UK,* i.d.wilkinson@sheffield.ac.uk

Diabetes and the Brain

Contents

I Update on Diabetes for Neurologists

1 Type 1 Diabetes

Edith W.M.T. ter Braak and Aline M.E. Stades

CONTENTS

ABSTRACT

Type 1 diabetes is a life long metabolic disorder that is characterized by absolute insulin deficiency resulting in hyperglycemia and lipolysis. Type 1 diabetes accounts for 5–10% of the total diabetes population, the majority of the other patients has type 2 diabetes. Insulin deficiency originates with autoimmune mediated β-cell destruction. Without insulin treatment, type 1 diabetes leads to dehydration and ketoacidosis and can ultimately be fatal. Prolonged exposure to hyperglycemia is responsible for microvascular damage in the eye, kidneys and nervous system and contributes to macrovascular disease of the coronary, cerebral and peripheral arteries. Limited joint mobility and the diabetic foot are other complications related to chronic hyperglycemia. Currently, the corner stone of the treatment of type 1 diabetes is exogenous insulin substitution aiming to restore near-normal glycemia in order to prevent or delay long-term complications. Recurrent hypoglycemia is a frequent complication and a serious burden for both patients and their significant others. Additional therapeutic interventions consist of lifestyle modifications, particularly aiming

From: *Contemporary Diabetes: Diabetes and the Brain*
Edited by: G. J. Biessels, J. A. Luchsinger (eds.), DOI 10.1007/978-1-60327-850-8_1

to reduce cardiovascular risk factors. In the future,the necessity for substitution with exogenous insulin may be replaced by β-cell transplantation or even preventive β-cell preservation. Patients must receive proper education and support, since they have to manage their chronic disease on a daily basis.

Key words: Type 1 Diabetes; Insulin; Ketoacidosis; Hyperglycemia; Hypoglycemia; Autoimmune; β-cells; Long-term complications; Education; Self-care.

INTRODUCTION

The current classification of diabetes in different subtypes is based on the defect(s) that causes hyperglycemia, namely, aberrant or deficient insulin secretion or insufficient insulin action *(1)*. Type 1 diabetes (T1D) originates from autoimmune-mediated destruction of the pancreatic β-cells that normally produce insulin, thus resulting in absolute insulin deficiency. Other types of pancreatic disease involving destruction of the β-cells, such as alcoholic pancreatitis, are classified otherwise. Previously, T1D was also known as juvenile-onset diabetes or insulin-dependent diabetes mellitus (IDDM). However, these expressions may result in misclassification and indistinct prognosis and therapeutic options. Criteria to diagnose T1D are shown in Table 1 *(1)*. Note that diagnostic criteria do not include HbA1c levels, which are exclusively used to follow glycemic control, but not diagnosis.

Table 1
Diagnostic criteria for diabetes mellitus (ADA)

Diabetes mellitus (overall)
Symptoms of polyuria, polydipsia, unexplained weight loss
or
Random plasma glucose ≥ 11.1 mmol/l (200 mg/dl) on 2 subsequent days
or
Fasting (>8 h) plasma glucose ≥ 7.0 mmol/l (126 mg/dl) on 2 subsequent days
Type 1 diabetes mellitus
Autoantibody GAD positive and/or autoantibody tyrosine phosphatase IA-2/IA-2β
or
Presenting with ketoacidosis
Additional criteria for diabetes mellitus type 1 (used for research purposes)
Fasting C-peptide <0.1 nmol/l
2 mg Glucagon IV-stimulated C-peptide < 0.3 nmol/l

Adapted from ADA Position Statement *(23)* and an interpretation of data from Service et al. *(63)*.

EPIDEMIOLOGY

Several studies report T1D incidence numbers of 0.1–36.8/100,000 subjects worldwide *(2)*. Above the age of 15 years ketoacidosis at presentation occurs on average in 10% of the population; in children ketoacidosis at presentation is more frequent *(3, 4)*. Overall, publications report a male predominance (1.8 male/female ratio) and a seasonal pattern with higher incidence in November through March in European countries. Worldwide, the incidence of T1D is higher in more developed countries *(1, 2, 4–6)*. Throughout the last decades the overall incidence of T1D has not changed. Recent reports from several European countries, however, suggest that the median age at diagnosis decreased over the last decades. After asthma, T1D is a leading cause of chronic disease in children.

A diagnosis of T1D at the age of 30 or above was formerly referred to as latent-onset autoimmune diabetes in adults (LADA). This is not infrequent and it is estimated that about 10% of the population with a phenotype of type 2 diabetes actually had (autoimmune-mediated) T1D *(7)*. This specific population has anti-GAD or IA-2 antibodies by definition, albeit that in the first 6 months to 6 years after diagnosis these patients do not depend on insulin and that part of them is overweight resulting in concomitant (relative) insulin resistance. In this particular subpopulation, β-cell destruction is only slowly progressive and may take up to 12 years to be complete. An association of the occurrence of T1D with viral infections in early childhood or with vaccination could not be confirmed in recent studies *(8)*.

PATHOPHYSIOLOGY

Genetics and Autoimmunity

T1D is a cell-mediated autoimmune disease with destruction of β-cells that are located in the pancreatic islets of Langerhans. Several islet cell autoantibodies have been isolated: glutamic acid decarboxylase (GAD) and tyrosine phosphatases IA-2 and IA-2β. The majority of type 1 diabetic patients (75–95%) have positive autoantibodies at the time of manifestation. In addition, observations in families have shown an association with the HLA complex, especially the class 2 molecules, suggesting a predominant role in aberrances in T-cell-mediated responses via cytotoxic and helper T cells *(6)*. T1D is strongly associated with HLA DQA and DQB genes, but this can differ among various populations throughout the world. In contrast, twin studies show a low concordant prevalence of T1D of only 30–55%.